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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/919,506 | 07/31/2001 | John G. Babish | T8638.NP | 2768 |

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| EXAMINER | |
|---|---|
| PATTEN, PATRICIA A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1654 | |

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/919,506 | BABISH ET AL. | |
| | Examiner | Art Unit | |
| | Patricia A Patten | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *21-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 43-57* is/are rejected.

7)☒ Claim(s) *16-20 and 58-62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1- 62 are pending in the application.

Claims 11-42 were withdrawn from consideration on the merits in the response filed 11/15/02. New claims 43-62 are directed toward the elected invention and are hereby examined along with claims 1-10. It is further noted that claims 11-20 have been rejoined for examination on the merits. In the previous Office Action, the Examiner noted that the elected invention (whereby claims 16-20 are solely drawn to the elected invention) was withdrawn from the merits. It was communicated to Applicants that this invention was not found in the prior art, and therefore should have been listed as claims under examination. This was an inadvertent error. These claims (16-20) are not found in the prior art and do not have any other outstanding rejections. However, please note that they are objected to for being dependant upon a rejected claim (please see 'Allowable Subject Matter' *infra*). With regard to claims 11-15, these claims were also examined on the merits along with claims 1-10, 16-20 and 43-62.

Claims 1-20 and 43-62 were examined on the merits.

Applicant's arguments were persuasive. The previous rejections are hereby removed. However, it has been deemed that a new rejection is in order.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 and 43-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, it has been found that there are hundreds of species of sesquiterpene lactones, and possibly hundreds of species of diterpene lactones and triterpene lactones, please see for example the Phytochemical Dictionary (PD) which lists 207 sesquiterpene lactone species.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor(s) had possession of the claimed invention. See, *e.g., Vas-Cath, Inc.* v.*Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. However, a showing of possession alone does not cure the lack of a written description. *Enzo*

*Biochem, Inc.* v.*Gen-Probe, Inc.*, 296 F.3d 1316, 1330, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). In the Instant case, Applicants have not provided any evidence that they were actually in possession of every sesquiterpene lactone which is listed in the PD which is evidence that Applicants were also not in possession of every combination of sesquiterpene lactone and diterpene lactone or alternatively every combination of sesquiterpene lactone and triterpene lactone. Thus, it is deemed that Applicants have not provided adequate support which would verifiably indicate that they had in their possession, at the time the Instant application was filed, every combination of sesquiterpene lactone and diterpene lactone, or sesquiterpene lactone and triterpene lactone.

"[A]reduction to practice does not occur until the inventor has determined that the invention will work for its intended purpose."); Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572,1578, 38 USPQ2d 1288, 1291 (Fed. Cir. 1996). Here, Harborne specifically states:

> "Among other structural modifications of sesquiterpene lactones, the incorporations of hydroxyl groups, e.g., anistatin or esterfied hydroxyl groups, e.g., arcitopicrin or epoxy rings, e.g., canin, are common. A few lactones occur in the glycosidic form, e.g., paucin, and some contain halogens, e.g., chlorohyssopifolin A or aromatic substituents, e.g., lactopicrin. There is also the possibility of dimerisation, as in the case of absinthin, which is a guaianolide dimer. At least 4000 lactones have now been described, the great majority of which have been obtained from a single plant family, the Compositae..." (p.654).

It is not found convincing, that Applicants have indeed contemplated or reduced to practice every combination of sesquiterpene lactone along with diterpene lactones or triterpene lactones based on the evidence of the multitude of sesquiterpenes known in the art, as described by Harborne.

Claims 1-15 and 43-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for inhibition of inducible COX-2 activity and having minimal effect on COX-1 activity comprising parthenolide in combination with andrographolide, ursolic acid or oleanolic acid, does not reasonably provide enablement for combination of every sesquiterpene lactone in combination with any diterpene lactone or any triterpene lactone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to

make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The Instant specification as filed does not include a teaching of how to make and use the full scope of the claimed invention. There are no specifics or examples of how to make any composition which would perform as intended besides the combination of elements which are parthenolide, as the first component, and a compound selected from the group consisting of andrographolide, ursolic acid and oleanolic acid, as the second component.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to

pharmaceutically acceptable compositions and to methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments.

For both adequate disclosure and/or enablement requires representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention. See *In re Riat et al.* CCPA 1964 327 F2d 685, 140 USPQ 471; *In re Barr et al.* CCPA 1971 444 F2d 349, 151 USPQ 724, for enablement and for disclosure see Court of Appeals for the Federal Circuit decision, The Regents of the University of California v. Eli Lilly and Company which can be found at the Federal Circuit web site, www.fedcir.gov as file 96-1175.

It has been established that Applicants were not in possession of the full scope of the claimed invention (*supra*). Applicants further have not provided any evidence that combinations besides parthenolide, as the first component, and a compound selected from the group consisting of andrographolide, ursolic acid and oleanolic acid, as the second component for treating COX-2 related impairments would work commenserate in scope with the claimed invention. As indicated in PD, there are hundreds of known sesquiterpene lactones all having respective structures and functions. Because sesquiterpene lactones all have respective structures and functions, they are

unpredictable in nature. One sesquiterpene lactone will not provide the same effects, *in-vitro* or *in-vivo* as another. Therefore, in order to practice the claims within the full scope if their intent, the skilled artisan would need to perform undue experimentation in order to ascertain what other combinations of sesquiterpene lactones/diterpene lactones or sesquiterpene lactones/diterpene lactones besides what is actually shown in the specification would prove even relatively effective.

Lacking such guidance in the Instant specification with regard to any other combination of sesquiterpene lactones/diterpene lactones besides parthenolide, as the first component, and a compound selected from the group consisting of andrographolide, ursolic acid and oleanolic acid, as the second component, one would need to consult the prior art in order to determine if one would have a reasonable expectation that the compounds would be effective in such combinations. However, compositions which comprise sesquiterpene lactones in combination with diterpene lactones or triterpene lactones for inhibition of COX-2 activity are not well known in the art, and therefore, the Examiner cannot draw to the prior art in order to supplement the teachings in the Instant specification.

*In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are

insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, ***scope of enablement varies inversely with degree of unpredictability of factors involved***." (emphasis added)

Accordingly, the vast breadth of the claims is not sufficiently supported by ample guidance within the specification of how to make and use such compositions. The prior art **does not provide the artisan any reasonable expectation** that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed. Therefore, to practice the invention according to the full breadth of the claims would require not just a repetition of work, on the contrary, since Applicants have only disclosed one working embodiment, however, would require time consuming trial and error protocols in order to determine the functionality of the plethora of possible combinations of elements presented in the claims.

***Allowable Subject Matter***

Claims 16-20 and 58-62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A Patten whose telephone number is (571) 272-0968. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0968. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patricia A Patten
Examiner
Art Unit 1654

3/31/04

PATRICIA PATTEN
PATENT EXAMINER